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Studies in the Field of Organophosphorus Insecticides

T. A. Mastryukova

(Institute for Hetero-Organic Compounds, Moscow)

The present study was carried out in the laboratory of organophosphorus compounds under the direction of the Corresponding Member of the Academy M.I.Kabachnik. The studies in the field of insecticides were begun in 1952 and at first had a nonsystematic character, but from 1953 and especially from 1954 numerous organophosphorus compounds were synthesized in our laboratory with the purpose of obtaining new insecticides.

In 1953 there was established a constant contact with V.I.Z.R. of V.A.S.Kh.N.I.L. where the tests of insecticidal properties of our compounds were made. This contact was expressed not only by the transfer of substances for tests but also, and this was very important, in a systematic discussion with the workers of V.I.Z.R. - D.M.Paikin, M.P.Shabanova and N.M.Gamper - of the results of the tests and means of preparing new active compounds. A similarly friendly contact we were able to establish with the representatives of the chemical industry. S.L.Varshavskii and S.V.Preobrazhenskaya aided in many ways the successful completion of the present work. Part of the work was carried out in the laboratory of vinyl compounds of the Institute of Organic Chemistry of the Academy of Sciences (M.F.Shostakovskii, E.N.Prilezhaeva) and in the laboratory for organic synthesis of V.N.I.I.V. M.P.T.Sh.P. (V.N.Odnoralova).

In order to have a possibility of selection among the uncountable number of existing and possible organic substances of a definite and necessarily limited number of objects for the tests, it is necessary to be guided by some working hypothesis which permits one to carry out such a selection consciously and with aim.

In our studies we used the rather well accepted working hypothesis concerning the inhibition of cholinesterase as the cause of the toxic action of organophosphorus insecticides and concerning the acylating action of organophosphorus insecticides on the cholinesterase of insects as the chemical mechanism of this inhibition.

Insofar as at this time it is probable (1) that the object of phosphorylation in this enzyme is the hydroxyl group of serine which enters the polypeptide chain of its molecules, the working hypothesis was

refined in that the selection was made among organophosphorus compounds which are capable of phosphorylating the alcoholic hydroxyl group having some noticeable but weak acidic properties. Such organophosphorus compounds may be the anhydrides of acid esters of phosphorus acids, acid halides, substances similar to acid halides but containing, in the molecule, some pseudohaloid groups instaed of the halogens, and, finally, neutral esters of acids of phosphorus in which one of the alkyl groups would correspond sufficiently well to an acidic alcohol. Since the acid halide and the anhydride derivatives of acids of phosphorus, as well as phosphorus esters of phenols, to which one may assign, without stretching the point, some functions of mixed anhydrides, have been already studied in detail and are being intensively studied in other laboratories, we concentrated our attention on the derivatives of acids of phosphorus which have residues of sufficiently acidic alcohols or mercaptans.

Further, we refined our working hypothesis in the sense that we realized the necessary presence in the molecule of an effective insecticide of a certain optimum amount of the phosphorylating properties. Organophosphorus compounds with sharply displayed phosphorylating action as for instance dialkyl chlorophosphates, naturally cannot be sufficiently selective agents since they would show their phosphorylating action with any substrate of the organism: unspecific proteins, carbohydrates and, finally, water. Such substances would be very rapidly detoxified in the organism and would not reach those vitally important centers, the phosphorylation of which would be the consequently following toxic effect. On the other hand substances having but feeble phosphorylating properties such as neutral esters of phosphoric or thiophosphoric acids, although able to reach the necessary receptors without large losses, would be able to react then with the latter so slowly, if at all, that no action would result.

Therefore in the process of synthetic searches, when we found a poorly physiologically active substance, as an insecticide, with weak phosphorylating properties (slow hydrolysis, reactions with alcohols, amines), we along along the path of such a change in the structure of the molecule as to strengthen these properties. Conversely, if an insufficiently active (as an insecticide) substance turns out to be a good phosphorylating agent, we went along the route of such a change of its structure which would yield an analog which would be less active.

The above shown principles were naturally not adhered to very firmly. The chemical distinction between the true cholinesterase, the inactivation of which assures the poisoning of warm blooded animals, and the

pseudo-cholinesterase or the insect cholinesterase is still not clear. We know too little about the mechanism of toxic action to depend with complete confidence on the accepted working hypothesis. However, by being guided by these principles we built in general lines the plans for our syntheses and some positive results which we obtained were too systematic to be purely the work of chance.

Many literature data permit us to conclude that there is sense in searches in the area of thiophosphate compounds. The latter are distinguished from their oxygen analogs by lower toxicity to warm blooded animals with preservation of the effective properties in respect to the insects.

In order to run the syntheses of substances with various structures it was necessary first of all to develop reasonable methods of preparation of the starting materials.

The majority of the known methods of synthesis of thio-organophosphorus compounds are mainly based on the chloride derivatives of phosphorus. The latter are often inconvenient in handling and during the work with them it is necessary as a rule to conduct out of the zone of the reaction, by some means, the hydrogen chloride which forms in the reaction.

Thio-organophosphorus compounds can be prepared also from the sulfides of phosphorus. Sulfides are cheap, simple in handling and their production is well in hand. Therefore we stopped with the sulfides of phosphorus as the initial starting base for the syntheses of thioorganophosphorus compounds.

Back in 1950 we explored the reactions of phosphorus sulfides P_4S_5, P_4S_6 and P_4S_7 with alcohols (2)

$$\begin{matrix} P_4S_6 \\ P_4S_5 \end{matrix} \xrightarrow{ROH} (RO)_2P(S)H + (RO)_2P(S)SR$$

$$P_4S_7 \xrightarrow{ROH} (RO)_2P(S)H + (RO)_2P(S)SH + (RO)_2P(S)SR$$

It had been established that lower sulfides of phosphorus P_4S_5 and P_4S_5 react with alcohols forming dialkyl thiophosphites and trialkyl dithiophosphates. The phosphorus sulfide P_4S_7 forms in its reaction a mixture of three substances which may be separated in a usual fractional distillation into dialkyl thiophosphites, dialkyl dithiophosphates and trialkyl dithiophosphates. The only exception is the reaction of this sulfide with methyl alcohol as the result of which there are formed but two compounds: dimethyl thiophosphite and trimethyl dithiophosphate. As to the mechanism of the reaction of the lower sulfides of phosphorus

with alcohols, this appears to be a complex one. We examined the reaction of the sulfide P_4S_7 with ethyl alcohol: along with the three products indicated above, there are also formed hydrogen sulfide, phosphine and phosphorus. It is very probable that all these products form as the result of not a single reaction but of several which run in parallel. The hydrolysis of P_4S_7 is similarly complex in its course.

We also studied (4) the previously known (5) products of the reaction of phosphorus decasulfide P_4S_{10} with alcohols:

$$P_4S_{10} + 8ROH \rightarrow 4\ (RO)_2P(S)SH + 2H_2S.$$

In this way there were developed the preparatively accessible methods of synthesis starting with phosphorus sulfides of dialkyl thiophosphites, derivatives of trivalent phosphorus which were obtained in this work for the first time, dialkyl dithiophosphates and trialkyl dithiophosphates. Here were prepared for the first time in pure state the free dialkyl dithiophosphates.

The constants of the compounds prepared by us in these three classes of substances were used by us for the calculation of atomic refractions of sulfur bound to the phosphorus in the thiono and the thiolo type of linkage (6,7). The knowledge of the atomic refraction of sulfur was later of considerable help in the synthesis of compounds of predetermined structures.

These three classes of compounds were the first objects tested for insecticidal action. All turned out to be weakly toxic to insects. Their tests, as with all subsequent objects, were run on adult specimens of Eurygaster taken from the site of hibernation, and on the pest of citrus plants - the Marine flour worm. In the system of nomenclature used in the present report (table 1) one plus means that 95-100% of dead and paralyzed insects were observed after the action of the compound taken in concentration of 0.3% or greater. Two pluses correspond to the minimum lethal concentration of 0.1%, three pluses - 0.05%, etc. as shown in the table. The results of tests of the first three groups of compounds are shown in tables 2, 3 and 4.

As can be seen, dialkyl thiophosphites, dialkyl dithiophosphates and trialkyl dithiophosphates were poorly effective substances. From the dialkyl dithiophosphates we prepared and tested their potassium and nickel salts. These were also poor insecticides. If one compares these three classes of compounds, the most effective of them are dialkyl thiophosphites, derivatives of trivalent phosphorus.

Table 1.

Insecticidal action of organophosphorus compounds on insects (95-100% kill).

Concentration, %	Notation
0.3	+
0.1	++
0.05	+++
0.005	++++
0.0005	+++++

Table 2

Constants and insecticidal action of tested preparations

No.	Preparation	Formula	B.Pt. °C p in mm.	n_D^{20}	d_4^{20}	Action
1	M-1	$(MeO)_2PHS$	52-3/17	1.4768	1.1892	+
2	M-4	$(EtO)_2PHS$	67-8/12	1.4597	1.0828	+
3	M-7	$(PrO)_2PHS$	62-3/3	1.4581	1.0290	-
4	M-9	$(iso\text{-}PrO)_2PHS$	49-50/3	1.4541	1.0135	+
5	M-13	$(BuO)_2PHS$	89-90/4	1.4583	0.9974	-
6	M-15	$(CH_2{:}CHCH_2O)_2PHS$	77-8/6	1.4911	1.0894	+

The work on the synthesis of insecticides proper was begun with the prepartion of the simplest derivatives of dithiophosphoric acid. There were prepared disulfides of the general formula $(RO)_2P(S)SSA$, where A may be the simplest alkyl radical or a residue of dithiophosphoric acid. The former were prepared by the reaction of salts of dialkyl dithiophosphates with sulfenyl chlorides (6) (this study was performed with the participation by the collaborator of our laboratory E.I.Godyny) :

$$(RO)_2P(S)SM + R'SCl \rightarrow (RO)_2P(S)S\text{-}SR' + MCl$$

$$2(RO)_2P(S)SM + I_2 \rightarrow (RO)_2P(S)S\text{-}SP(S)(OR)_2 + 2\ MI,$$

while the latter compounds were prepared by oxidation of the same salts by a solution of iodine (8). The resulting disulfides were tested both in the form of emulsions as well as dusts. However they also turned out to be rather weak insecticides (table 5). The compounds cited were but weak phosphorylating agents. They are very stable, are hydrolyzed with difficulty and are sufficiently stable in respect to alkalies. "e had to go on thus to the more labile anhydride forms.

As such we selected the acyl derivatives of dialkyl dithiophosphoric acids. These were prepared in good yields from sodium, potassium and lead salts of the corresponding acids and acyl halides (7).

$$(RO)_2P(S)SM + R'COCl \rightarrow (RO)_2P(S)SCOR' + MCl$$

$$(RO)_2P(S)SNa + R'COOCl \rightarrow (RO)_2P(S)SCOOR' + NaCl.$$

Table 3

Constants and insecticidal action of the prepared substances

No.	Prepn.	Formula	B.pt °C p in mm	M.pt. °C	n_D^{20}	d_4^{20}	Action
1	M-3	$(MeO)_2PSSH$	62-3/5	-	1.5343	1.2888	-
2	M-5	$(EtO)_2PSSH$	81-2/5	-	1.5070	1.1654	+
3	M-8	$(PrO)_2PSSH$	85-6/3	-	1.4987	1.1040	-
4	M-11	$(iso\text{-}PrO)_2PSSH$	71-2/3	-	1.4918	1.0911	+
5	M-36	$(iso\text{-}BuO)_2PSSH$	93/4	-	1.4889	1.0558	-
6	-	$(EtO)_2PSSK$	-	194-5	-	-	+
7	-	$[(EtO)_2PSS)_2]Pb$	-	75-6	-	-	-
8	-	$[(MeO)_2PSS]_2Ni$	-	124-5	-	-	+

Table 4

Constants and insecticidal action of the tested compounds

No.	Prepn.	Formula	B.pt °C p mm.	n_D^{20}	d_4^{20}	Action
1	M-2	$(MeO)_2PS(SMe)$	101/17	1.5292	1.2415	-
2	M-6	$(EtO)_2PS(SEt)$	115/10	1.5013	1.1168	+
3	M-9	$(PrO)_2PS(SPr)$	115-6/3	1.4955	1.0561	-
4	M-12	$(iso\text{-}PrO)_2PS(SPr\text{-}iso)$	91-2/3	1.4843	1.0351	-
5	M-14	$(iso\text{-}BuO)_2PS(SBu\text{-}iso)$	148-9/4	1.4859	1.0159	+

Table 5

Constants and insecticidal action of tested compounds.

No.	Prepn.	Formula	B.pt.	M.pt.	n_D^{20}	d_4^{20}	Action
1	M-44	$(EtO)_2PS_3Me$	101-2/3	-	1.5500	1.2142	+
2	M-48	$(EtO)_2PS_3Et$	106-7/3	-	1.5431	1.1810	+
3	M-49	$(EtO)_2PS_3Bu$	139-40/4	-	1.5306	1.1246	+
4	M-43	$(iso\text{-}PrO)_2PS_3Me$	99-100/2	-	1.5297	1.1471	+
5	M-50	$(iso\text{-}PrO)_2PS_3Et$	117-8/3	-	1.5240	1.1189	+
6	M-52	$(iso\text{-}BuO)_2PS_3Et$	129-30/3	-	1.5183	1.0866	+
7	M-16	$[(MeO)_2PSS]_2$	-	51-2	-	-	-
8	M-1[illegible]	$[(EtO)_2PSS]_2$	-	28-9	-	-	-
9	M-18	$[(iso\text{-}PrO)_2PSS]_2$	-	91-2	-	-	-

It is of interest to note that the acetyl derivatives are obtained with equal success from the potassium and sodium, as well as lead salts of dialkyl dithiophosphoric acids. The benzoyl derivative may be prepared only from the lead salt. In turn the carbonate derivatives could be obtained only from the salts of the alkali metals. As it is evident from table 6, the acyl derivatives prepared by us turned out to be more effective poisons, but still left much to be desired.

Even more active phosphorylating agents should be the oxygen analogs of the above cited acyl derivatives. These are constructed like the above compounds but contain one less atom of sulfur than the corresponding derivatives of dialkyl dithiophosphoric acids:

$$(RO)_2P(S)OAcyl \qquad (RO)_2P(O)SAcyl$$

However, the chemistry of these compounds is but poorly explored. The synthesis of acyl derivatives from the salts of dialkyl thiophosphoric acids required special work on clarification of the reactivity of these. The results of this work may be expressed by the following scheme:

$$(RO)_2P(S)OM \begin{array}{l} \rightarrow (RO)_2P(O)SR \\ \rightarrow (RO)_2P(S)OCOR' \\ \rightarrow (RO)_2P(O)SCOOR' \end{array}$$

Table 6

Constants and effectiveness of action of acyl derivatives

No.	Prepn.	Formula	B.pt.	n_D^{20}	d_4^{20}	Action
1	M-25	$(EtO)_2PS_2COMe$	98/2	1.5154	1.1898	+
2	M-26	$(iso\text{-}PrO)_2PS_2COMe$	100-1/3	1.4979	1.1177	-
3	M-38	$(iso\text{-}BuO)_2PS_2COMe$	125-6/3	1.4929	1.0793	-
4	M-39	$(iso\text{-}PrO)_2PS_2COPh$	m.51-2	-	-	-
5	M-27	$(EtO)_2PS_2CO_2Me$	105-6/4	1.5063	1.2171	+
6	M-29	$(EtO)_2PS_2CO_2Et$	115/4	1.5001	1.1891	+
7	M-30	$(EtO)_2PS_2CO_2Pr$	125/6	1.4981	1.1620	+
8	M-34	$(EtO)_2PS_2CO_2Bu$	162-3/6	1.4889	1.1281	-
9	M-31	$(EtO)_2PS_2CO_2Am$	137-8/4	1.4925	1.1179	-
10	M-32	$(iso\text{-}PrO)_2PS_2CO_2Et$	109/3	1.4894	1.1301	-
11	M-33	$(iso\text{-}PrO)_2PS_2CO_2Am$	138/3	1.4841	1.0773	-

During the study of the reactions of alkylation and acylation of the sodium, potassium and silver salts of dialkyl monothiophosphoric acid we established the dual character of reaction of these salts. In the reaction of alkyl halides (8) the alkylation occurred at the sulfur atom (see the reaction scheme), while in acetylation -at the oxygen atom (9). The

Chlorocarbonate esters reacted with the [illegible] thiolo derivatives.

By means of the infrared spectra we established the structure of the alkali and the silver salts of dialkyl monothiophosphoric acids. For the alkali salts we confirmed the data of Gore who had found that they have the thiono structure. The spectra of the silver salts were determined by us for the first time. These speak of the thiolo structure of the salt with strong association of the molecules]

$$(RO)_2\overset{O\;\cdots\cdots\cdots\cdots AgS}{\underset{S-Ag\cdots\cdots\cdots O}{P}}P(OR)_2$$

The data concerning the structure of the salts in the absence of their tautomerism which is apparently improbable in this case speak of the fact that their reactions of alkylation and acylation may proceed with or without the transfer of the reactive center. This study was made in connection with work in the area of tautomerism and reactivity of organophosphorus compounds and is described in more detail in the report by M.I.Kabachnik.

Tests of the acyl derivatives of thiolophosphoric acid showed that these are weak insecticides. Similarly poorly effective turned out to be some of the alkyl derivatives (table 7). Strong insecticidal properties are had in the carbonate derivatives[their effectiveness is such that they cause a 95-100% kill of the flour worm after use in the concentration of 0.05% or greater (table 7, substances 6-7).

We also prepared mixed alkyl phosphoric disulfides from the corresponding sodium salts of dialkyl monothiophosphoric acid]

$$(RO)_2P(S)ONa + R'SCl \rightarrow (RO)_2P(O)S-SR' + NaCl.$$

and sulfenyl chlorides (8). The thus obtained derivatives showed high toxicity to the Eurygaster insect, especially substance M-51. For us this was a certain degree of success, although substance M-51 is less active than Tiofos in its contact action.

Thus, it seemed that monothiophosphoric derivatives give more chances for success in finding practically interesting substances. However, we did not consider it rational to develop this area insofar as it is being studied in many other laboratories.

A further study was directed along two main paths: 1) preparation of derivatives of the simplest alkyl-thiophosphonic acids and 2) the synthesis of trialkyl dithiophosphates containing definite substituents in predominantly the β-positions.

Alkyl-thiophosphonic derivatives may, judging from literature data, be more powerful inhibitors of cholinesterase than the corresponding

thiophosphoric derivatives.

Among the derivatives of alkyl-thiophosphonic acids we studied the dialkyl esters of alkylthiolophosphonic and alkylthionophosphonic acids (10). These substances were prepared by the action of alkyl halides on dialkyl thiophosphite sodium salt. For preparation of the thiolo derivatives, the thiono forms were isomerized by heating in a sealed tube in the presence of alkyl halides, according to Pishchimuka method. The thiolo derivatives were also prepared from the appropriate halides of alkylphosphonic acid and alcohol or mercaptan, as well as by alkylation of the alkali salts of esters of alkylthionophosphonic acids (this work was carried out with participation of the degree aspirant N.I.Kurochkin and E.E.Kugucheva).

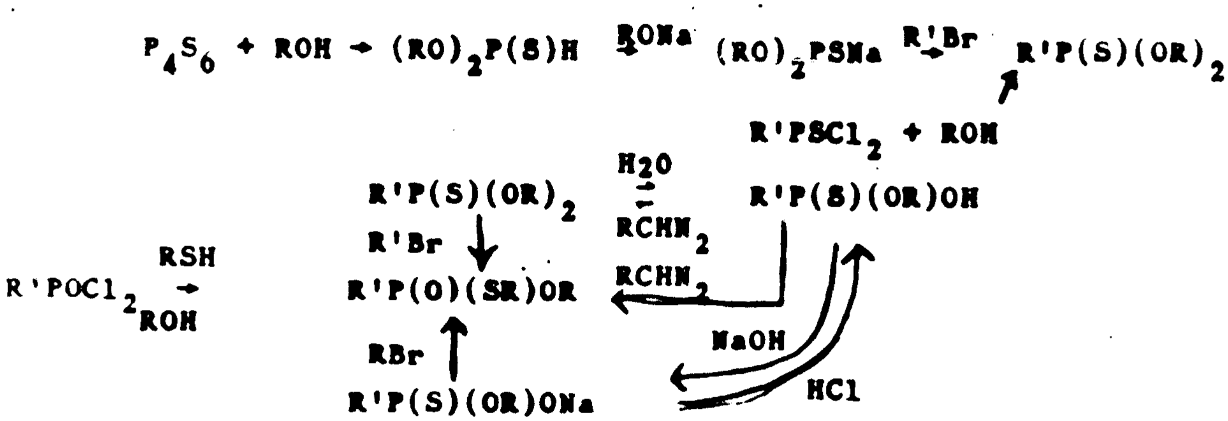


Table 8

Constants and insecticidal action of the tested compounds.

No.	Prepn.	Formula	B.pt.	n_D^{20}	d_4^{20}	Action
1	K-2	$MePS(OEt)_2$	76-8/13	1.4610	1.0553	+
2	K-19	EtPS(OMe)(OEt)	74-5/10	1.4665	1.0647	-
3	M-21	$EtPS(OEt)_2$	80-3/10	1.4576	1.0324	-
4	K-3	$PrPS(OEt)_2$	64-6/2	1.4596	1.0158	-
5	K-4	$BuPS(OEt)_2$	74-7/2	1.4600	1.0004	-
6	K-5	$PhCH_2PS(OEt)_2$	123-6/2	1.5305	1.1031	+
7	K-10	$MePS(OBu)_2$	72-4/1	1.4535	0.9843	-
8	K-11	$EtPS(OBu)_2$	80-3/2	1.4533	0.9775	-
9	K-22	EtPS(OEt)(OCOMe)	68-9/1.5	1.4701	1.1232	+

The first representatives of this group of substances were prepared by us back in 1950(M-24). The thiono and the thiolo esters (tables 8-9) differ considerably in the insecticidal properties. While the thiono esters, as should be expected, were only rather weak insecticides, the thiolo derivatives turned out to be quite effective. Thus, substances M-24, K-6 and K-9 were quite close to Tiofos.

By this path we first reached effective insecticides which along with the contact action also possessed the systemic action. However, none of the compounds possessed properties superior to the known insecticides in use now.

Somewhat different considerations lay in the foundation of the second path. I remind you that disulfide derivatives turned out to be too stable while the acyl derivatives, conversely, were too labile in order to make good insecticides. We stopped on the trialkyl dithiophosphates which carry substituents in the alkyl group connected with sulfur, especially in the β-position. We expected of these derivatives the optimum phosphorylating ability. Naturally only the experimental method could be used to prove this expectation.

Thus, by the reaction of ethylene oxide with dialkyl dithiophosphates we (together with the degree aspirant at V.N.I.I.V V.N.Odnoralova) prepared β-hydroxy derivatives

$$(RO)_2PS(SCH_2CH_2OH) \xrightarrow{PCl_5} (RO)_2PS(SCH_2CH_2Cl)$$

$$(RO)_2P(S)SH \xrightarrow{CH_2-CH_2-O} (RO)_2PS(SCH_2CH_2OH)$$

$$(RO)_2P(S)SH \xrightarrow{C_2H_4Cl_2} (RO)_2PS(SCH_2CH_2Cl)$$

$$(RO)_2P(S)SH \xrightarrow{CH_2-CH_2-NH} (RO)_2P(S)SCH_2CH_2NH_2$$

and from these we prepared β-acetoxy and β-chloro derivatives (11). We also prepared β-aminoethyl dithiophosphate, previously prepared in V.I.Z.R. in the A.I.Kulikov's laboratory. There were prepared other β-amino esters, as well as their derivatives. If one compares the activity effectiveness of compounds shown in table 10 it is easy to see that the introduction of substituents in the β-position increases the insecticidal properties in this series apparently along with the electronegativity of the substituents. The most active was the chloro derivative which had been prepared by Schrader (12).

The next step should be the synthesis of sulfur analogs

$$(RO)_2P(S)SCH_2CH_2SR'$$

especially since at that time there had appeared the patent of Schrader (13) on Systox, which is a β-substituted derivative of monothiophosphoric acid. At first it was proposed to use for the synthesis of β-alkylmercapto substituted compounds the reaction of addition of dialkyl dithiophosphates to vinyl thio ethers (this work was carried out in collaboration with Coworkers of Institute of Organic Chemistry M.F.Shostakovskii E.N.Prilezhaeva and N.N.Uvarova).

Table 9

Constants and insecticidal action of the compounds tested

No.	Prepn.	Formula	B.pt.	n_D^{20}	d_4^{20}	Action
1	K-9	MePO(SEt)(OEt)	106-8/18	1.4718	1.0904	+++
2	Ku-1	MePO(SEt)(OPr)	71-2/3	1.4510	1.0356	+
3	Ku-3	MePO(SEt)(OPr-iso)	60-2/1	1.4749	1.0555	++
4	Ku-2	MePO(SEt)(OBu-iso)	69-70/1	1.4666	1.0222	++
5	K-23	MePO(SCH_2OMe)(OEt)	117-20/2	1.4778	1.1538	+(+)
6	K-18	EtPO(SMe)(OEt)	93/9	1.4790	1.1058	+(+)
7	MO-24	EtPO(SEt)(OEt)	66-8/2.5	1.4747	1.0670	+++
8	K-12	EtPO(SBu)(OBu)	92-4/2	1.4660	0.9951	-
9	K-6	PrPO(SEt)(OEt)	85-6/3	1.4733	1.0447	++
10	K-7	BuPO(OEt)(SEt)	98-100/3	1.4728	1.0262	+
11	K-8	$PhCH_2PO$(SEt)(OEt)	134-6/2	1.5350	1.1263	+

Table 10

Constants and insecticidal action of the compounds tested

No.	Prepn.	Formula	B.pt. at 2 mm.	n_D^{20}	d_4^{20}	Action
1	MO-5	$(MeO)_2PS_2C_2H_4OH$	-	1.5380	1.2911	+
2	MO-1	$(EtO)_2PS_2C_2H_4OH$	119-20	1.5250	1.2042	+
3	MO-2	$(PrO)_2PS_2C_2H_4OH$	124-6	1.5140	1.1440	+
4	MO-4	$(iso\text{-}PrO)_2PS_2C_2H_4OH$	118-9	1.5083	1.1323	-
5	MO-3	$(iso\text{-}BuO)_2PS_2C_2H_4OH$	135-8	1.5045	1.0965	+
6	MO-6	$(EtO)_2PS_2C_2H_4OAc$	135-6	1.5010	1.1845	++
7	MO-7	$(iso\text{-}BuO)_2PS_2C_2H_4OAc$	140-1/1	1.4890	1.0948	+
8	MO-9	$(EtO)_2PS_2C_2H_4Cl$	103-4	1.5230	1.2270	+++
9	MO-14	$(EtO)_2PS_2C_2H_4NH_2$	-	1.5287	-	-
10	MO-19	$(PrO)_2PS_2C_2H_4NH_2$	-	1.5130	1.1099	-
11	MO-21	$(iso\text{-}BuO)_2PS_2C_2H_4NH_2$	-	1.5065	1.0705	-
12	MO-18	$(EtO)_2PS_2C_2H_4NH_2$ (picrate)	m.p.102-3	-	-	-

However it appeared that under the usual conditions there are not formed the β- ~~but~~ the α-derivatives, the structure of the addition products being determined by a known synthesis from α-chlorodiethyl sulfide as shown in the following scheme, and by other means (14).

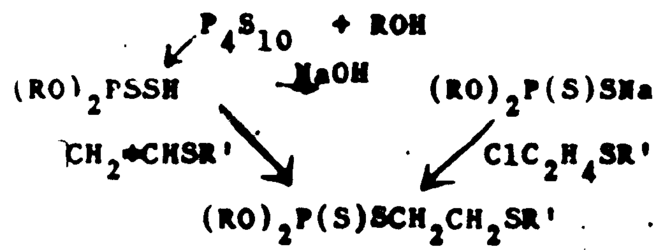
$(RO)_2PSSH$ + CH_2O, RSH $\rightarrow (RO)_2P(S)SCH_2SR'$ $\leftarrow$ $ClCH_2SR'$

+ KOH $\longrightarrow (RO)_2P(S)SK$

+ $CH_2{=}CHSR' \rightarrow (RO)_2P(S)SCHMeSR'$ $\leftarrow$ ClCHMeSR'

The substances prepared were tested on the Eurygaster insects. They turned out to be weak insecticides against this insect (table 11).

The synthesis of the first representatives of β-alkylmercapto substituted trialkyl dithiophosphates was achieved by us in 1953 in good yield of about 90-5% starting with sodium or potassium salts of dialkyl dithiophosphoric acids and β-chloroalkyl sulfides:



The latter were prepared in the beginning of the study by the reaction of hydrogen chloride with products of addition of mercaptans and vinyl ethers. The substances proved to be highly effective insecticides with contact-systemic action, exceeding by many orders the eisting organophosphorus chemical poisons (table 12). Therefore in the course of the following study we found a new and better method of synthesis, based on ethylene oxide, ethyl mercaptan and dialkyl dithiophosphoric acid.

Table 11

Constants and insecticidal properties of the compounds tested

No.	Prepn.	Formula	B.pt.	n_D^{20}	d_4^{20}	Action
1	M-65	$(EtO)_2PS_2CHMeSEt$	109-10/3	1.5290	1.1392	+
2	M-54	$(EtO)_2PS_2CHMeSBu$	109-10/2	1.5198	1.0965	+
3	M-59	$(EtO)_2PS_2CHMeSC_2H_4OBu$	123-5/3	1.5125	1.0940	+
4	M-56	$(iso\text{-}BuO)_2PS_2CHMeSEt$	113-5/2	1.5070	1.0556	+
5	M-55	$(iso\text{-}BuO)_2PS_2CHMeSBu$	121-2/2	1.5070	1.0384	+
6	M-53	$(iso\text{-}BuO)_2PS_2CHMeSC_2H_4OBu$	124-6/3	1.5012	1.0422	+
7	M-86	$(EtO)_2PS_2CH_2SPr$	145-6/4	1.5270	1.1308	-
8	M-87	$(EtO)_2PS_2CH_2SPr\text{-}iso$	133-4/4	1.5210	1.1312	-

Table 12.

No.	Prepn.	Formula	B.pt.	n_D^{20}	d_4^{20}	Action
1	M-82	$(MeO)_2PS_2C_2H_4SMe$	71-1.5/0.004	1.5580	1.2493	+++++
2	M-81	$(MeO)_2PS_2C_2H_4SEt$	91-2/0.003	1.5598	1.2065	++++
3	M-80	$(EtO)_2PS_2C_2H_4SMe$	127-8/2	1.5405	1.1699	++++
4	M-74	$(EtO)_2PS_2C_2H_4SEt$	129-30/2	1.5350	1.1445	+++++
5	M-85	$(EtO)_2PS_2C_2H_4SPr$	143-4/2	1.5275	1.1260	+++
6	M-77	$(EtO)_2PS_2C_2H_4SBu$	150/1	1.5255	1.1040	++
7	M-75	$(iso\text{-}PrO)_2PS_2C_2H_4SEt$	134-5/3	1.5189	1.0887	++
8	M-76	$(iso\text{-}PrO)_2PS_2C_2H_4SBu$	148-9/4	1.5106	1.0622	+
9	M-58	$(EtO)_2PS_2C_2H_4SC_2H_4OBu$	188/3	1.5160	1.1050	+++
10	M-78	$(iso\text{-}PrO)_2PS_2C_2H_4SC_2H_4OBu$	172-3/2	1.5090	1.0967	+

E.N.Prilezhaeva also realized the addition of dialkyl dithiophosphates to thiovinyl ethers contrary to the Markovnikov rule in the presence of isopropylbenzene hydroperoxide. Here there were formed β-substituted trialkyl dithiophosphates in 50-60% yields.

Tests of properties of compounds of this type xxxxxxx were conducted mainly with the specimen M-74. These tests were run on various plant cultures with several species of insects. Substance M-74 turned out to be a highly effective poison against the red apple mite, and at concentration of 0.05% protected the apple trees for up to a month and a half. M-74 remained effective up to two months against the Tetranychus mite on roses. At this concentration substance M-74 was effective up to three weeks against the green plum aphid. The duration of action of the substance in many experiments was greater than for Merkaptofos on the same objects.

Especially promising is the preseeding treatment of summer wheat grains. Seeds treated with 2% solution of the M-74 concentrate (with 30% content of the active substance) yield sprouts which are poisonous to Eurygaster for 2-3 weeks (100% kill). The norm of consumption of the substance is 120-150 grams of the active principle of M-74 per hectare of the field which fact shows the highly economic feature of M-74*

Interesting data, requiring further tests, were obtained in control of pests of sugar beet, corn, etc.

Not less interesting are substances M-81 and M-82. Their study was run on smaller scale than that of M-74. These are also contact-systemic insecticides. In effectiveness they are very close to M-74. However these compounds are weakly toxic to warm-blooded animals in comparison with ...aptofos or M-74. On intravenous application to rabbits they are almost ... times less toxic than Tiofos. Thus, as the result of the study we ...d in finding a group of insecticides - β-alkylmercaptoethyl esters ...kyl dithiophosphoric acid, which have high insecticidal and ...tivity with contact and systemic action.

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Remarks

(A.E.Arbuzov Chem.Inst., Kazan Section, Academy of ...

T.A.Mastryukova illustrated well the meaning of synthesis ...phorus insecticides on the basis of phosphorus sulfide, since ...e is very cheap and in addition has great possibilities for diverse synthesis.

...s made in the area of thiophosphoric compounds are only ... these studies.

Yakovlev (Brain Institute, Acad.Med.Sciences USSR)

... reports the speakers already have touched upon the ... ion of active centers of enzymes. At this time the ... in this area. The results given by T.A.Mastryukova justif... th of development of the previous study of the action ... rasic substances. For the reaction of insecticides with ... the phosphorylation reaction must proceed. For clari... as to which functional groups in the molecule of ... phosphorylated, modern means of study were used (chrom... ...ctive phosphorus) by means of which it was possible to ... phosphoric acid in yield of 40%. This is a proof ... of cholinesterase the hydroxyl group is phosphorylated. If serine as such, its hydroxyl group does not react with ... insecticides. It is necessary to say that all these studies ... development stage.

...Kagan (Kiev Institute for Labor Hygiene and Occup...)

... Mazur and Bodansky it is known that the mechanism of ... true and pseudo cholinesterases differs. Therefore ... the account of action of the insecticide on pseudo and ... cholinesterases. In addition it is desirable to show in the table ... ratio of action of the compounds on warm blooded animals and on ... This ratio would be of more use than insecticidal action alone.

N.I.Mel'nikov (Fertilizer and Insectofungicide Res.Inst. ... after Ya.V.Samoilov, Moscow)

I have no confidence in the fact that biologists consider the ... secticide acts only on cholinesterase. It seems to me that the ... cannot be solved in such single-valued manner. There are sub... inhibit cholinesterase and at the same time are not insecti... example such is the series of quaternary ammonium bases. ... of synergism raised by A.E.Arbuzov: addition of small amounts ... substances sometimes aid the elevation of toxicity by 2-3 fold. ... true of DDT and other insecticides. At this time the study of ... tures is being carried out very extensively.

V.A.Yakovlev (Brain Institute, Academy of Med.Sciences U...

The problem of antagonism and synergism of organophosphorus insecticides is not being worked on sufficiently. One should request the Biolo... Institute of the Academy of Sciences USSR to occupy itself with this pro...
